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Cervical cancer with ≤5 mm depth of invasion and >7 mm horizontal spread — Is lymph node assessment only required in patients with LVSI?

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HIGHLIGHTS

- The necessity of pelvic lymph node assessment in microinvasive cervical cancer depends on LVSI and histological subtype
- Lymph node assessment is essential in any tumour with LVSI
- Lymph node assessment can be omitted in squamous cell carcinoma without LVSI
- Lymph node assessment can be omitted in adenocarcinoma with <3 mm depth of invasion
- Lymph node assessment can be omitted in tumours without LVSI and with <3 mm depth of invasion

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ABSTRACT

Objective. Cervical cancer with ≤5 mm depth of invasion and >7 mm horizontal spread is classified FIGO IA instead of FIGO IB in the revised staging system, as horizontal spread is no longer considered. We aimed to determine the incidence of lymph node metastasis (LNM) and, consequently, the necessity of pelvic lymph node assessment.

Methods. Patients diagnosed between January 2015 and May 2019 with cervical cancer FIGO (2009) stage IB with ≤5 mm depth of invasion and >7 mm horizontal spread, were identified from the Netherlands Cancer Registry. Associations between disease-characteristics and lymph node metastasis (LNM), and overall survival, were assessed.

Results. Of 170 patients, six (3.5%) had LNM: 4/53 (7.6%) with adenocarcinoma and 2/117 (1.7%) with squamous cell carcinoma ($p = .077$). Four-year overall survival was 98.2%. LNM was observed more often in tumours with LVSI (4/43 patients, 9.3%) than without LVSI (2/117 patients, 1.7%) ($p = .045$). In adenocarcinoma with 3–5 mm depth of invasion LNM rate was 10% (4/40). None of the following tumours were observed with LNM: squamous cell carcinoma without LVSI (0/74); adenocarcinoma with <3 mm depth of invasion (0/13); <3 mm depth of invasion without LVSI (0/36).

Conclusions. Lymph node assessment is essential in any tumour with LVSI or in adenocarcinoma with 3–5 mm depth of invasion. It can be omitted in squamous cell carcinoma without LVSI, in adenocarcinoma with <3 mm depth of invasion and in any tumours without LVSI and with <3 mm depth of invasion.

1. Introduction

In 2018, the International Federation of Gynaecology and Obstetrics (FIGO) staging system for cervical cancer has been revised [1,2]. From now on, horizontal spread is no longer considered in determining FIGO stage for cervical cancer with ≤5 mm depth of invasion. One major consequence is that patients with these tumours, without

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invasion beyond the uterus and with >7 mm horizontal spread, will now be staged as FIGO IA instead of IB.

For FIGO (2009) stage IB, surgical treatment requires the addition of pelvic lymphadenectomy, as the risk of lymph node metastasis (LNM) is high (12.2%–29.8% [3–6]). In patients with stage IA the decision to perform a lymphadenectomy mainly depends on the presence of lymphovascular space invasion (LVSI). The clinical significance of LVSI in tumours with ≤5 mm depth of invasion has been a subject of debate for decades [7]. Its presence might affect the treatment plan, even though it has no role in the FIGO classification [2,8]. Gynaecologic oncologists might consider refraining from lymphadenectomy in patients with stage IAI and stage IA2 without LVSI, because of the low risk of LNM (0.1% and 1.3%, respectively), avoiding overtreatment and additional morbidity [7,9]. For patients with LVSI, lymphadenectomy is always recommended because of the high risk of LNM (12.0%) [9].

This study aimed to retrospectively evaluate the incidence of LNM in tumours with ≤5 mm depth of invasion and >7 mm horizontal spread, to determine whether they are likely to benefit from pelvic lymph node assessment. Moreover, the association between LVSI, histological subtype and LNM is examined.

2. Methods

2.1. Study design and patient selection

A nationwide retrospective cohort study was performed by analysing data from the Netherlands Cancer Registry (NCR), a population-based registry with coverage of all newly diagnosed malignancies in the Netherlands since 1989. The registration clerks routinely extract patient information from medical records within hospitals. They all undergo the same extensive training, using one coding manual specifically developed for cervical cancer, creating uniformity in data interpretation and entry. Data on vital status and date of death, obtained from the municipal demography registries, were available until January 2019.

All patients newly diagnosed with FIGO (2009) IB cervical cancer between January 2015 and May 2019, were identified from the NCR. Included were adenocarcinoma or squamous cell carcinoma, with: ≤5 mm depth of invasion and >7 mm horizontal spread. Patients were excluded if: no lymph nodes were examined; neoadjuvant chemo (radio)therapy was administered; data on depth of invasion or horizontal spread were missing. Data were collected by the registration clerks on patient and disease-related characteristics (including age at diagnosis, FIGO stage, histological subtype, differentiation grade, depth of invasion, LVSI, number of examined lymph nodes, number of positive lymph nodes, primary treatment and all-cause mortality). Pathology specimens were reviewed by a gynaecological pathologist.

2.2. Statistical analysis

Descriptive statistics were used to describe characteristics and the presence of LNM. Associations between LNM and qualitative variables were assessed using Fisher's exact test, whereas quantitative variables were assessed by the Mann–Whitney *U* test. The Kaplan–Meier method was applied to calculate overall survival. All analyses were performed using Stata/SE version 14.2 (Stata Corporation, College Station, TX, USA). Statistical tests were two-tailed and considered significant at $p < .05$.

3. Results

Of the 3803 patients diagnosed with cervical cancer between January 2015 and May 2019, 170 (4.5%) met the inclusion criteria (Fig. 1). Patient and disease-related characteristics are presented in Table 1. Median age at diagnosis was 39 (range 26–76 years). After a median

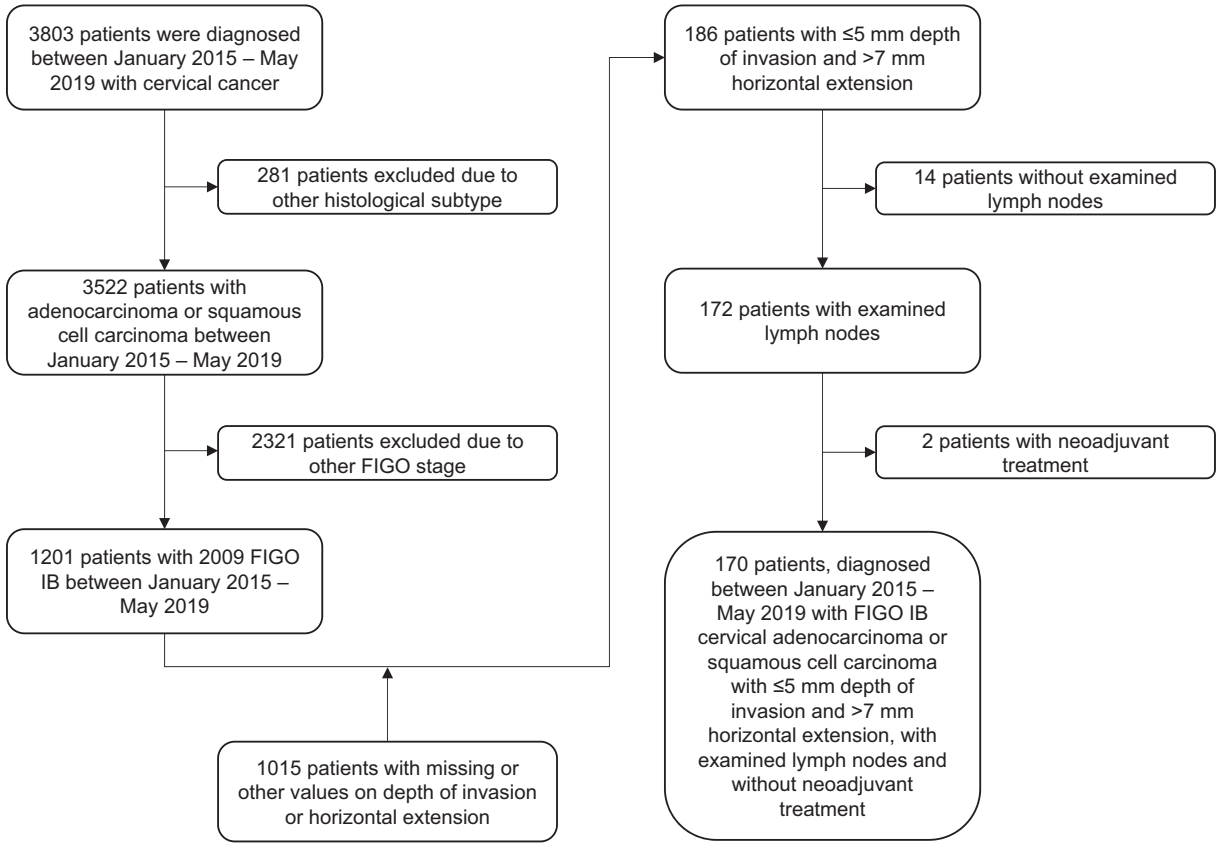

Fig. 1. Patient selection flowchart.

Table 1
Characteristics of 170 cervical cancer patients (2009 FIGO stage IB) with tumours with ≤5 mm depth of invasion and >7 mm horizontal extension, organised by presence of lymph node metastasis.

Characteristics, *n* (%)	Missing		Full cohort ($N = 170$)		LNM, no ($n = 164$; 96%)		LNM, yes ($n = 6$; 4%)		P[a]
Age, years[b]			39	(26–76)	39	(26–76)	35	(27–55)	0.55
Primary treatment									0.06
Surgery			161	(95)	156	(95)	5	(83)	
Chemoradiation			1	[1]	0	(0)	1	(17)	
Conisation			8	[5]	8	[5]	0	(0)	
Histological subtype									0.08
Squamous cell carcinoma			117	(69)	115	(70)	2	(33)	
Adenocarcinoma			53	(31)	49	(30)	4	(67)	
Differentiation grade	48	(28)							0.33
1			17	(14)	16	(14)	1	(20)	
2			63	(52)	62	(53)	1	(20)	
3			42	(34)	39	(33)	3	(60)	
Lymph nodes examined[b]			22	(2–57)	22	(2–57)	19	(9–37)	0.32
Lymph nodes positive[b]			0	(0–2)	–		2	(1–2)	
Depth of invasion									0.47
<3 mm			47	(28)	46	(28)	1	(17)	
3–5 mm			123	(72)	118	(72)	5	(83)	
Lymphovascular space invasion	10	[6]	43	(27)	39	(25)	4	(67)	0.05
Follow-up, months[b]			19	(0–49)	19	(0–49)	25	(10—30)	0.76
All-cause mortality	7	[4]	2	[1]	2	[1]	0	(0)	0.93

LNM lymph node metastasis. Because of rounding, percentages might not sum to 100%.
[a] Mann-Whitney *U* test for continuous variables, Fisher's exact test for categorical variables.
[b] Median (range).

follow-up duration of 19 months, two patients (1.2%) had died, resulting in a 4-year overall survival rate of 98.2%.

Squamous cell carcinoma was the most prevalent histological subtype (68.8%) and most of the tumours had an invasion depth of 3–5 mm (72.4%). LVSI was confirmed in 26.9% of the tumours, with higher rates in squamous cell carcinoma compared to adenocarcinoma (32.1% vs. 15.7%, $p = .035$). The median number of examined lymph nodes was 22, ranging from 2 to 57.

Six of the 170 patients (3.5%) had pathologically confirmed LNM. Stratified by invasion depth, LNM was detected in 1/48 patients (2.1%) with <3 mm depth of invasion and in 5/130 (3.9%) with 3–5 mm depth of invasion ($p = .49$). Comparing histological subtypes, 4/53 patients (7.6%) with adenocarcinoma and 2/117 (1.7%) with squamous cell carcinoma were observed with LNM ($p = .08$). LNM was confirmed in four of the patients with LVSI (9.3%), which was significantly more often than in patients without LVSI ($n = 2$; 1.7%), $p = .045$.

Analyses on common histological subtypes, depth of invasion and LVSI in relation to LNM, are shown in Table 2. A decision tree for lymph node assessment, combining these characteristics, is presented in Fig. 2. LNM was confirmed in 0/13 patients (0.0%) with <3 mm depth of invasion and adenocarcinoma and 4/40 patients (10.0%) with 3–5 mm depth of invasion and adenocarcinoma ($p = .56$). None of the 36 patients (0.0%) with <3 mm depth of invasion without LVSI, had LNM. Of the patients with adenocarcinoma and LVSI, 2/8 (25.0%) had LNM, next to 2/35 patients (5.7%) with squamous cell carcinoma and LVSI ($p = .15$). None of the 74 patients (0.0%) with squamous cell carcinoma without LVSI had LNM.

4. Discussion

Our results have important implications for the treatment of patients with cervical cancer with ≤5 mm depth of invasion and >7 mm horizontal spread. We found the incidence of pathologically confirmed LNM, and consequently the benefit of lymph node assessment, to be associated with LVSI and histological subtype.

A large retrospective study by Bean et al. [10] on oncological outcome after stage IA cervical cancer, included 5749 patients with squamous cell carcinoma and 1567 with adenocarcinoma. They found low rates of LNM (<1.0%) in both histological subtypes and suggest that these patients may not benefit from pelvic lymphadenectomy. However, the authors argue to take into account LVSI in this decision, as its presence is associated with LNM – an association which has been demonstrated previously [9,11,12]. In a review by van Meurs et al. on 535 patients with stage IA2 cervical cancer [9], tumours with LVSI were observed with a 12.0% LNM rate, versus 9.3% in our study. LNM rates were markedly lower in those with LVSI (1.3%), similar to our study (1.7%). Van Meurs et al. [9] reported an association between histological subtype and LNM. They found low rates of LNM in

Table 2
Depth of invasion, histological subtypes and LVSI[a], related to lymph node metastasis.

Characteristics, *n* (%)	Total	Depth of invasion ($n = 170$)				P[b]
		<3 mm	LNM, yes	3–5 mm	LNM, yes	
Histological subtype						
SC	117	34 (29)	1 (3)	83 (71)	1 (1)	0.50
AC	53	13 (25)	0 (0)	40 (75)	4 (10)	0.56
LVSI						
Yes	43	10 (23)	1 (10)	33 (77)	3 (9)	1.00
No	117	36 (31)	0 (0)	81 (69)	2 (2)	1.00
Characteristics, *n* (%)	Total	Histological subtype ($n = 170$)				P
		SC	LNM, yes	AC	LNM, yes	
Depth of invasion						
<3 mm	47	34 (72)	1 (3)	13 (28)	0 (0)	1.00
3–5 mm	123	83 (67)	1 (1)	40 (33)	4 (10)	0.04
LVSI						
Yes	43	35 (81)	2 (6)	8 (19)	2 (25)	0.15
No	117	74 (63)	0 (0)	43 (37)	2 (5)	0.13
Characteristics, *n* (%)	Total	LVSI ($n = 160$)				P
		LVSI, yes	LNM, yes	LVSI, no	LNM, yes	
Depth of invasion						
<3 mm	46	10 (22)	1 (10)	36 (78)	0 (0)	0.22
3–5 mm	114	33 (29)	3 (9)	81 (71)	2 (2)	0.15
Histological subtype						
SC	109	35 (32)	2 (6)	74 (68)	0 (0)	0.10
AC	51	8 (16)	2 (25)	43 (84)	2 (5)	0.11

SC squamous cell carcinoma; AC adenocarcinoma; LVSI lymphovascular space invasion; LNM lymph node metastasis.
[a] Missing values LVSI 6%, $n = 10$.
[b] Fisher's exact test.

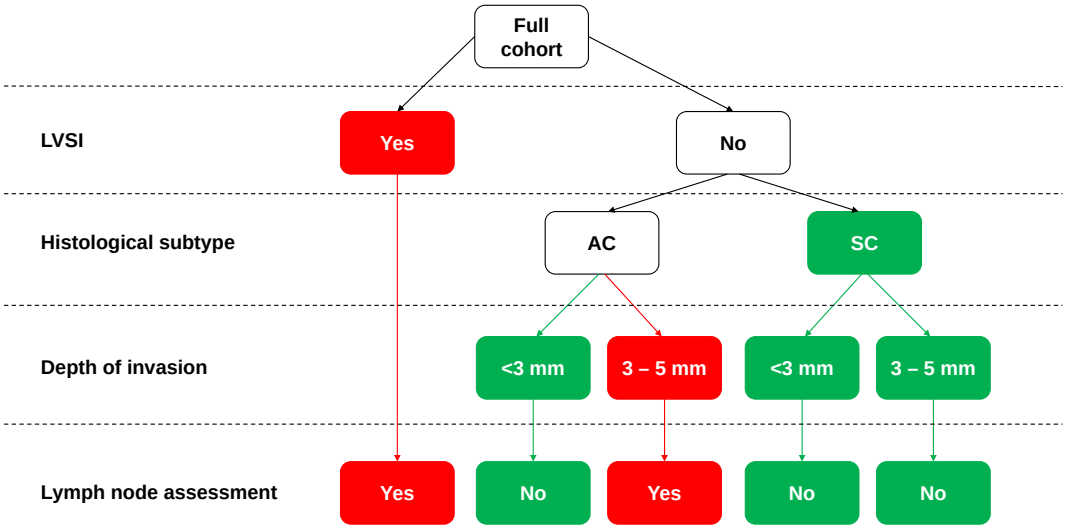

Fig. 2. Lymph node assessment decision tree. LVSI lymphovascular space invasion; AC adenocarcinoma; SC squamous cell carcinoma.

adenocarcinoma (0.3%) and only recommended pelvic lymphadenectomy for tumours with squamous cell carcinoma (LNM rate 3.3%), next to any tumour with LVSI. In our study, relatively high rates of LNM were observed in adenocarcinoma (7.5%), especially in combination with LVSI (25.0%). In adenocarcinoma without LVSI, LNM was observed in 4.7%. Moreover, all adenocarcinoma with LNM had 3–5 mm depth of invasion. For squamous cell carcinoma, LNM was only associated with the presence of LVSI: 0.0% in tumours without LVSI and in 5.7% tumours with LVSI. Although the sample size and number of events hamper statistical testing to reach significance in our study, LNM seems to be associated with LVSI and histological subtype in tumours with ≤5 mm depth of invasion and >7 mm horizontal spread.

Current guidelines recommend a pelvic lymphadenectomy in FIGO IA cervical cancer to detect LNM, except for stage IA1 without LVSI. The incidence rate of LNM in our study (3.5%) justifies the question whether lymphadenectomy, with risk of significant morbidity, is advisable in stage IA tumours with >7 mm horizontal spread. Sentinel lymph node detection has been proposed as alternative procedure, with less morbidity, to identify LNM. A review by Tax et al. [13] on FIGO IA2, IB1 and IIA1 cervical cancer, reported the highest sensitivity and negative predictive value in of patients with bilateral sentinel lymph node detection and without suspicious lymph nodes pre- and perioperatively. The authors argued a residual risk of occult metastasis of 0.08% in this group, corresponding to 1/1275 patients, sufficient to replace a full pelvic lymphadenectomy by a sentinel lymph node procedure.

For stage IA without LVSI, a trend towards more conservative treatment is discernible. Consequently, these patients may be treated by a general gynaecologist, but only after being discussed in a multidisciplinary team, including review by a specialised pathologist. As this is a part of daily practice in the Netherlands, we deem it possible, but unlikely, that patients in our cohort were undertreated.

The strength of this study is the use of the Netherlands Cancer Registry, providing a nationally representative sample of the Dutch population, reflecting daily practice. Although a highly specific group of patients was examined, a relatively large sample was included for analysis. Its limitation lies in the retrospective data collection, which heavily relies on the quality of data in medical records and reports of pathology laboratories. One major limitation lies in the number of events from which our conclusions were derived. The limited number of patients with LNM indicates that our study results require validation.

In conclusion, LNM was detected in 3.5% of the patients with cervical cancer with ≤5 mm depth of invasion and >7 mm horizontal spread. Lymph node assessment is essential in any tumour with LVSI or in adenocarcinoma with 3–5 mm depth of invasion. It can be omitted in squamous cell carcinoma without LVSI, in adenocarcinoma with <3 mm depth of invasion and in any tumours without LVSI and with <3 mm depth of invasion.

CRediT authorship contribution statement

Hans H.B. Wenzel: Conceptualization, Methodology, Software, Formal analysis, Validation, Investigation, Data curation, Writing - original draft, Visualization. **Kim G.G. Van Kol:** Methodology, Formal analysis, Investigation, Writing - original draft. **Hans W. Nijman:** Conceptualization, Writing - review & editing. **Valery E.P.P. Lemmens:** Writing - review & editing. **Maaike A. Van der Aa:** Conceptualization, Writing - review & editing. **Renée M.F. Ebisch:** Writing - review & editing. **Ruud L.M. Bekkers:** Conceptualization, Methodology, Writing - review & editing.

Declaration of competing interest

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